β-Blockers and vascular hemodynamics in patients with peripheral arterial disease

Schlager, Oliver ; Gajdosova Kovacicova, Ludmila ; Senn, Oliver ; Amann-Vesti, Beatrice ; Wilkinson, Ian B ; Jacomella, Vincenzo ; Husmann, Marc

Abstract: Aortic augmentation index (AIx) is a marker of central aortic pressure burden and is modulated by antihypertensive drugs. In patients with peripheral arterial disease (PAD) undergoing antihypertensive treatment, aortic pressures parameters, heart rate-adjusted augmentation index (AIx75), and unadjusted AIx were determined. The (aortic) systolic and diastolic blood pressure did not differ between PAD patients who were taking β-blockers (n=61) and those who were not taking β-blockers (n=80). In patients taking β-blockers, augmentation pressure and pulse pressure were higher than in patients who did not take β-blockers (augmentation pressure, P=.02; pulse pressure, P=.005). AIx75 was lower in PAD patients taking β-blockers than in patients not taking β-blockers (P=.04), while the AIx did not differ between PAD patients taking and not taking β-blockers. The present study demonstrates that β-blockers potentially affect markers of vascular hemodynamics in patients with PAD. Because these markers are surrogates of cardiovascular risk, further studies are warranted to clarify the impact of selective β-blocker treatment on clinical outcome in patients with PAD.

DOI: https://doi.org/10.1111/jch.12854

Beta blockers and vascular hemodynamics in patients with peripheral arterial disease

Running head: Beta blockers in peripheral arterial disease

Oliver Schlager, MD;[1] Ludmila Gajdosova Kovacicova, MD;[2]

Oliver Senn, MD, MPH;[3] Beatrice Amann-Vesti MD;[2]

Ian B. Wilkinson, MD, DM, FRCP, FAHA;[4] Vincenzo Jacomella, MD;[2]

Marc Husmann, MD[2]

[1]Division of Angiology, Department of Medicine II, Medical University of Vienna, Austria, [2]Clinic for Angiology, University Hospital Zurich, Switzerland, [3]Institute of Primary Care, University of Zurich, Switzerland, [4]Division of Experimental Medicine and Immunotherapeutics, University of Cambridge, Cambridge, United Kingdom

Word count abstract: 166

Word count text: 2420 (excluding abstract, references, tables and figures)

Corresponding author: Marc Husmann, MD, Clinic of Angiology, University Hospital Zurich, Raemistrasse 100, 8091 Zurich, Switzerland

Mail to: marc.husmann@usz.ch, Phone: +41442553491, Fax: +41442554510.

Coauthors' email addresses: oliver.schlager@meduniwien.ac.at; Ludmila.Gajdosova@ksb.ch; oliver.senn@usz.ch, beatrice.amann-vesti@usz.ch, v.jacomella@hin.ch, ibw20@medschl.cam.ac.uk

Abstract

Aortic augmentation index (AIx) is a marker of central aortic pressure burden and is modulated by antihypertensive drugs. In patients with peripheral arterial disease (PAD) and antihypertensive treatment aortic pressures parameters, the heart rate adjusted augmentation index (AIx75) and the unadjusted AIx were determined. The (aortic) systolic and diastolic blood pressure did not differ between PAD patients with beta blockers (n=61) and without beta blockers (n=80). In patients with beta blockers, augmentation pressure and pulse pressure were higher than in patients without beta blockers (augmentation pressure p=0.02, pulse pressure p=0.005). AIx75 was lower in PAD patients with beta blockers than in patients without beta blockers (p=0.04), while the AIx did not differ between PAD patients with and without beta blockers. In summary, the present study demonstrates that beta blockers potentially affect markers of vascular hemodynamics in patients with PAD. Because these markers are surrogates of cardiovascular risk, further studies are warranted to clarify the impact of selective beta blocker treatment on clinical outcome in patients with PAD.

1. Introduction

Peripheral arterial disease (PAD) is a common manifestation of advanced atherosclerosis. In industrialized countries PAD affects almost one fourth of the population over the age of 50 [1]. PAD is associated with a substantial increase in cardiovascular morbidity and mortality compared to healthy subjects [2]. Therefore, cardiovascular risk reduction is the primary goal in the therapeutic management of PAD patients.

In patients with clinically manifest atherosclerosis the central augmentation index (AIx) has emerged as independent predictor for the future occurrence of cardiovascular events [3]. The Aix constitutes the proportion between the second and first peak of the arterial pulse wave. It can be measured non-invasively by radial applantation tonometry. The AIx mainly depends on pressure wave reflections from peripheral arteries and peripheral arterial stiffness.

Peripheral arterial tone as well as wave reflections may potentially be influenced by antihypertensive medication. Previous data have shown that antihypertensive drugs can differently influence the arterial pulse wave morphology and the AIx [4]. Within the spectrum of antihypertensive drugs beta blockers are related to a higher AIx as consequence of their negative chronotropic properties [4]. In patients with PAD angiotensin-converting enzyme inhibitors (ACE-I) have been proposed to lower the AIx [5]. Whilst ACE-I have been well established as antihypertensive treatment in patients with PAD the use of beta blockers is controversially debated over the past years [6-8].

Up to now, there is no evidence that beta blockers adversely affect the peripheral arterial perfusion and PAD associated symptoms [9]. In particular, the impact of beta blockers on vascular hemodynamics in patients with PAD is still matter of discussion.

Hence, the aim of the present study was to assess differences in vascular hemodynamics between PAD patients with and without beta blocking treatment in the setting of a cross-sectional study.

2. Methods

2.1. Patients

Consecutive patients with stable PAD (Rutherford categories 0-3) who were referred to the Clinic of Angiology at the University Hospital Zurich were eligible for this study. Exclusion criteria comprised critical limb ischemia (Rutherford categories 4-6), the presence of an inflammatory vascular disease as well as cardiac arrhythmias.
The study was performed according to the recommendations of the Declaration of Helsinki and the ICH-GCP guidelines and the protocol was approved by the institutional ethical committee. Before inclusion written informed consent was obtained in all patients.

2.2. Clinical data

All patients underwent a complete clinical examination. Demographic data including patients' age, sex, body mass index (BMI), smoking habits as well as each patients' medication were systematically recorded. The diagnosis of PAD was established according to current guidelines [10]. Patients with PAD were clinically classified according to Rutherford's categories for PAD [11].
The presence of arterial hypertension and dyslipidemia were diagnosed referring to the respective guidelines [12, 13]. Diabetes mellitus was diagnosed in patients on continuous antidiabetic medication or in accordance with current recommendations for the diagnosis of diabetes [14]. The presence of coronary artery disease or cerebrovascular disease was declared upon the patients' medical history. Besides arterial hypertension, a history of coronary artery disease was an indication for the use of beta blockers and/or ACE-I/ARB.

2.3. Generation/class of beta blockers

For further differentiation beta blockers were stratified by generation [15]: first generation/nonselective beta blockers: propranolol; second generation/selective β_1 blockers: atenolol, metoprolol, bisoprolol, third generation/beta blockers with assumed vasodilating activity: carvedilol, nebivolol.

2.4. Hemodynamic measurements

Blood pressure and pulse wave analyses were performed in a quiet room with a constant room temperature after a resting period of 15 minutes. All measurements were obtained in a supine patient position.

As previously published, blood pressure measurements of the lower limbs were obtained using a hand-held 6-MHz Doppler probe (Kranzbühler, Logidop 2, Pilger Medical Electronics, Switzerland) and appropriate sphygmomanometer cuffs [16]. Thereby, the systolic blood pressures of the anterior and posterior tibial arteries were measured at the ankle of each patient's limb. Further, bilateral brachial blood pressure measurements were obtained in all patients. The ankle brachial index (ABI) for each leg was calculated as the ratio of the highest systolic ankle blood pressure of the respective side and the highest systolic brachial blood pressure of both sides. For further analyses the ABI of the most affected limb was used. Radial artery pressure waveforms were recorded by applanation tonometry using a high-fidelity micromanometer (Millar Instruments, Houston, TX, USA) [17]. The aortic pressure waveforms were derived from the radial pressure waveforms using the SphygmoCor software (AtCor Medical; Sydney Australia) and a generalized transfer function [18]. The (aortic) systolic blood pressure and the (aortic) diastolic blood pressure were determined from the aortic pressure waveforms. The (aortic) pulse pressure was calculated as difference between the systolic blood pressure and the diastolic blood

pressure. The (aortic) augmentation pressure constitutes the differences between the second and first peaks of the central (aortic) pressure waveform. The AIx [%] was calculated as ratio between the augmentation pressure and the pulse pressure. As main outcome parameter the AIx was adjusted to a heart rate of 75 bpm (AIx75). In addition, the unadjusted AIx was analyzed.

2.5. Statistical analysis

Continuous data are presented as mean ± standard deviation. Discrete data are given as counts and percentages. The primary endpoint was the difference in hemodynamic variables (AIx75, AIx, PP, augmentation pressure, aSBP, aDBP) between users and nonusers of the respective antihypertensive drugs (ACE-I, BB, CCB and diuretics). For study analyses ACE-I and angiotensin receptor blockers (ARB) were grouped as one class of antihypertensive drugs. For group comparisons an independent-samples t-test was run. Correlations were examined by calculating Pearson or Spearman-Rho correlations coefficients as appropriate. Multivariate linear regression analysis was used to further assess the independent association between bb intake and Aix75. A two-sided p-value <0.05 was considered statistically significant. Calculations were performed using SPSS for Mac (Version 20.0, SPSS Inc Chic., IL, USA).

3. Results

In total 141 patients with a mean age of 68.9 ± 10.5 years (90 males, 63.8 %) who were admitted to the Clinic of Angiology at the University Hospital Zurich were included into this cross sectional study. Of these 141 patients 45 patients (31.9%) were classified as Rutherford category 0, 33 patients (23.4%) were classified as Rutherford category 1 or 2 and 63 patients (44.7%) as Rutherford category 3. Included patients had a mean BMI of 25.5 ± 4 kg/m^2, 91 (64.5%) patients were diagnosed with dyslipidemia and 37 (26.2%) patients with type 2 diabetes mellitus. A history of arterial hypertension was present in 116 patients (82.3%), a history of coronary artery disease in 41 patients (29.1%).

Of the included 141 patients, 61 patients (43.3%) were on beta blockers (beta blockers of the first generation: 2 patients, beta blockers of the second generation: 49 patients, beta blockers of the third generation: 10 patients). Demographic and clinical data of patients, who were on beta blocker treatment, and patients without beta blockers are given in ***Table 1***.

3.1. Antihypertensive drugs and vascular hemodynamics

The AIx75 was lower in patients on beta blockers than in patients not taking beta blockers (p=0.04, ***Figure 1A***), while the (heart rate unadjusted) AIx did not differ between patients with and without beta blockers (***Figure 1B***). Heart rate (69 ± 10 bpm) was inversely related to the (heart rate unadjusted) AIx (p=-0.42, r<0.0001). In PAD patients the AIx75 was lower than the AIx (AIx75: 30.9 ± 7.8% vs. AIx: 33.7 ± 8.4%, p<0.0001). The difference between AIx75 and AIx was more pronounced in patients with beta blockers than in patients without beta blocker treatment (***Figure 2***). The generation of beta blockers was neither associated with the AIx75 (p=0.47, Spearman correlation coefficient r=0.1), nor with the (heart rate unadjusted) AIx

(p=0.94, Spearman correlation coefficient r=0.01). Further, the ABI (of the mainly affected limb) was neither related to the AIx75 (p=0.11, Pearson correlation coefficient r=-0.14), nor to the (unadjusted) AIx (p=0.23, Pearson correlation coefficient r=-0.16). The pulse pressure and the augmentation pressure were higher in patients taking beta blockers than in patients without beta blockers (***Table 2***). No significant difference in AIx75 and unadjusted AIx was found between patients who were on ACE-I/ARB, CCB and diuretics in comparison with patients without the respective antihypertensive drugs (***Figure 1A+B***). Patients who received ACE-I/ARB had higher systolic blood pressure values than patients who were not on that medication (***Figure 3A***). No differences of diastolic blood pressure values were observed between users and non-users of ACE-I/ARB, beta blockers, CCB and diuretics (***Figure 3B***).

3.2. Multivariate model

To account for potential confounders we included patients' age, sex, heights, smoking status, pulse pressure and use of other antihypertensive drugs (e.g. ACE-I/ARB, CCB, diuretics) in a multivariate model. In this model, beta blocker-treatment was still related to a significantly lower AIx75 (mean adjusted difference: -4.1; 95% CI -7.9, -0.3; p=0.04). In contrast ACE-I/ARB, CCB and diuretics were not related to the AIx75 in this model (ACE-I/ARB: mean adjusted difference 0.1; 95% CI -3.6, 3.9; p=0.94, CCB: mean adjusted difference -3.3; 95% CI -7.4, 0.8; p=0.11, diuretics: mean adjusted difference 0.3; 95% CI -3.3, 4; p=0.85).

4. Discussion

The main finding of the present study is that PAD patients taking beta blockers had a lower AIx75 compared to patients without beta blockers. Comparable differences were not found for the other main classes of antihypertensive drugs (ACE-I/ARB, CCB and diuretics).

In the therapeutic management of PAD adequate blood pressure control is an important aim. According to the reduction of cardiovascular events in the Heart Outcomes Prevention Evaluation (HOPE) study ACE-I have been established as preferred antihypertensive drug in PAD patients [6]. In the past, in PAD patients (early generation) beta blockers were avoided as antihypertensive drugs according to an allegedly unfavorable effect on peripheral perfusion [8]. However, concerns on the use of beta blockers in PAD were refuted by a meta-analysis with 11 randomized controlled studies, which showed that beta blockers did not adversely affect symptoms in patients, with mild to moderate peripheral perfusion deficits [19]. Regarding vascular hemodynamics another, more recent meta-analysis demonstrated an association between beta blockers and an increase in AIx in hypertensive patients [20]. It should be noted, however, that neither of these studies allows conclusions to be drawn with respect to the relation between beta blockers and the AIx in PAD patients.

Focusing on PAD patients the present study revealed a lower AIx75 in subjects receiving beta blockers than in those not taking them. In line with previous data, the AIx was inversely related to the heart rate in the present study [21]. Although the heart rate was lower in patients with beta blockers than in patients without beta blockers, the unadjusted AIx did not differ between both groups. It has to be noted, however, that adjustment for heart rate led to a decrease in AIx in patients with and without beta blockers. This might conjointly be attributed to the average heart rate,

which was below 75 bpm in the majority of included patients, as well as to the inverse correlation between heart rate and the AIx. In analogy to these associations the decline from AIx to AIx75 was more pronounced in patients with beta blockers (with a larger heart rate difference between baseline and the adjusted heart rate of 75 bpm) than in patients without beta blockers.

Interestingly, neither the ABI nor the generation of beta blocker was associated with the AIx75 in PAD patients. The comparably lower AIx75 in PAD patients with beta blockers stands in contrast to previous findings on the AIx in hypertensive patients [20]. Apart from the above mentioned impact of heart rate on the difference in AIx between patients with and without beta blockers two mechanisms could additionally contribute to beta blocker-associated differences of the AIx75: beta blocker affect the cardiac inotropy, which might consequently have an impact on the AIx75. Secondly, beta blocker might target the magnitude of peripheral pulse wave reflections.

Notably, the AIx75 is not a measure, but constitutes a ratio between the augmentation pressure and the pulse pressure. In the present study both components, the augmentation pressure and the pulse pressure, were higher in PAD patients taking beta blockers than in patients without beta blockers.

The pulse pressure itself constitutes the difference between the systolic and diastolic blood pressure. In the present study, the systolic blood pressure tended to be higher and the diastolic blood pressure tended to be lower in patients with beta blockers than in patients without beta blockers. Taken separately, the between-group differences in systolic and diastolic blood pressure were statistically not significant. However, these differences seem to sum up in the pulse pressure, which subsequently explains the higher pulse pressure in PAD patients with beta blockers than in patients without beta blockers.

Regarding other antihypertensive drugs, systolic blood pressure was higher in PAD patients with ACE-I than in PAD patients without ACE-I. Nevertheless, we found no significant difference in AIx between patients with and without ACE-I treatment. In purely arithmetical terms, this is a consequence of not only higher systolic blood pressure, but also higher diastolic blood pressure in patients with ACE-I of the present study.

The second component of the AIx75, the augmentation pressure, is a surrogate of wave reflection [22]. In the present study the augmentation pressure was higher in PAD patients with beta blockers than in those without beta blockers. However, the difference in augmentation pressure between patients with and without beta blockers was much less pronounced than the difference in pulse pressure. Accordingly, the ratio of both components – with the pulse pressure as denominator – led to the lower AIx75 in PAD patients with beta blockers.

The findings of the present study have to be viewed in the light of its limitations: first, the modest sample size of the present study has to be acknowledged. Although we detected significant differences in AIx75 between patients with and without beta blockers, we cannot exclude that a larger number of patients would have revealed further differences of other blood pressure lowering drugs. Secondly, this study is a cross-sectional study without follow-up measurements of the AIx75. Therefore, the proposed findings have to be interpreted with caution regarding a potential causal connection between the intake of beta blockers and the AIx75.

Nonetheless, the major strength of this investigation warrants mention: up to now, data on the impact of beta blockers on vascular hemodynamics in patients with PAD are scarce. To our knowledge, this is the first investigation showing a potential impact of beta blockers on vascular hemodynamics in patients with PAD. Nevertheless, further studies are required to clarify, whether the lower AIx75 and higher pulse and

augmentation pressures in PAD patients on beta blockers has an impact on clinical outcome.

Conclusion

In PAD, central aortic hemodynamics may be affected by beta blocker treatment. Additional studies are needed to clarify whether the association between beta blockers and vascular hemodynamics contributes to clinical outcome in PAD.

References

1 Hirsch AT, Halverson SL, Treat-Jacobson D, Hotvedt PS, Lunzer MM, Krook S *et al.* The Minnesota Regional Peripheral Arterial Disease Screening Program: toward a definition of community standards of care. *Vascular medicine (London, England)* 2001;**6**:87-96.

2 Criqui MH, Langer RD, Fronek A, Feigelson HS, Klauber MR, McCann TJ *et al.* Mortality over a period of 10 years in patients with peripheral arterial disease. *The New England journal of medicine* 1992;**326**:381-6.

3 Weber T, Auer J, O'Rourke M F, Kvas E, Lassnig E, Lamm G *et al.* Increased arterial wave reflections predict severe cardiovascular events in patients undergoing percutaneous coronary interventions. *European heart journal* 2005;**26**:2657-63.

4 Williams B, Lacy PS, Thom SM, Cruickshank K, Stanton A, Collier D *et al.* Differential impact of blood pressure-lowering drugs on central aortic pressure and clinical outcomes: principal results of the Conduit Artery Function Evaluation (CAFE) study. *Circulation* 2006;**113**:1213-25.

5 Ahimastos AA, Dart AM, Lawler A, Blombery PA and Kingwell BA. Reduced arterial stiffness may contribute to angiotensin-converting enzyme inhibitor induced improvements in walking time in peripheral arterial disease patients. *Journal of hypertension* 2008;**26**:1037-42.

6 Ostergren J, Sleight P, Dagenais G, Danisa K, Bosch J, Qilong Y *et al.* Impact of ramipril in patients with evidence of clinical or subclinical peripheral arterial disease. *European heart journal* 2004;**25**:17-24.

7 Mostafaie K, Bedenis R and Harrington D. Beta-adrenergic blockers for perioperative cardiac risk reduction in people undergoing vascular surgery. *The Cochrane database of systematic reviews* 2015;**1**:CD006342.

8 Lane DA and Lip GY. Treatment of hypertension in peripheral arterial disease. *The Cochrane database of systematic reviews* 2013;**12**:CD003075.

9 Paravastu SC, Mendonca DA and Da Silva A. Beta blockers for peripheral arterial disease. *The Cochrane database of systematic reviews* 2013;**9**:CD005508.

10 Tendera M, Aboyans V, Bartelink ML, Baumgartner I, Clement D, Collet JP *et al.* ESC Guidelines on the diagnosis and treatment of peripheral artery diseases: Document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteries: the Task Force on the Diagnosis and Treatment of Peripheral Artery Diseases of the European Society of Cardiology (ESC). *European heart journal* 2011;**32**:2851-906.

11 Rutherford RB, Baker JD, Ernst C, Johnston KW, Porter JM, Ahn S *et al.* Recommended standards for reports dealing with lower extremity ischemia: revised version. *J Vasc Surg* 1997;**26**:517-38.

12 Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Bohm M *et al.* 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *European heart journal* 2013;**34**:2159-219.

13 Reiner Z, Catapano AL, De Backer G, Graham I, Taskinen MR, Wiklund O *et al.* ESC/EAS Guidelines for the management of dyslipidaemias: the Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). *European heart journal* 2011;**32**:1769-818.

14 Diagnosis and classification of diabetes mellitus. *Diabetes care* 2010;**33 Suppl 1**:S62-9.
15 Bristow MR. beta-adrenergic receptor blockade in chronic heart failure. *Circulation* 2000;**101**:558-69.
16 Jacomella V, Shenoy A, Mosimann K, Kohler MK, Amann-Vesti B and Husmann M. The impact of endovascular lower-limb revascularisation on the aortic augmentation index in patients with peripheral arterial disease. *European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery* 2013;**45**:497-501.
17 Chen CH, Nevo E, Fetics B, Pak PH, Yin FC, Maughan WL *et al.* Estimation of central aortic pressure waveform by mathematical transformation of radial tonometry pressure. Validation of generalized transfer function. *Circulation* 1997;**95**:1827-36.
18 Pauca AL, O'Rourke MF and Kon ND. Prospective evaluation of a method for estimating ascending aortic pressure from the radial artery pressure waveform. *Hypertension* 2001;**38**:932-7.
19 Radack K and Deck C. Beta-adrenergic blocker therapy does not worsen intermittent claudication in subjects with peripheral arterial disease. A meta-analysis of randomized controlled trials. *Archives of internal medicine* 1991;**151**:1769-76.
20 Manisty CH and Hughes AD. Meta-analysis of the comparative effects of different classes of antihypertensive agents on brachial and central systolic blood pressure, and augmentation index. *British journal of clinical pharmacology* 2013;**75**:79-92.
21 Wilkinson IB, MacCallum H, Flint L, Cockcroft JR, Newby DE and Webb DJ. The influence of heart rate on augmentation index and central arterial pressure in humans. *The Journal of physiology* 2000;**525 Pt 1**:263-70.
22 Chirinos JA, Zambrano JP, Chakko S, Veerani A, Schob A, Willens HJ *et al.* Aortic pressure augmentation predicts adverse cardiovascular events in patients with established coronary artery disease. *Hypertension* 2005;**45**:980-5.

Conflicts of interest

There are no conflicts of interest in relation to that work.

Acknowledgments

The study has been supported by grants from the Swiss Heart Foundation and

Matching Funds of the University Hospital of Zurich (both to Marc Husmann).

Figure legends

Figure 1

Bar charts (means) and respective error bars (± 2SE) illustrating the **(A)** heart rate adjusted (75 bpm) aortic augmentation index (AIx75), **(B)** the unadjusted aortic augmentation index (AIx) in patients with peripheral arterial disease receiving/not receiving angiotensin-converting enzyme inhibitors (ACE-I)/angiotensin receptor blockers (ARB), beta blockers, calcium channel blockers (CCB) and/or diuretics.

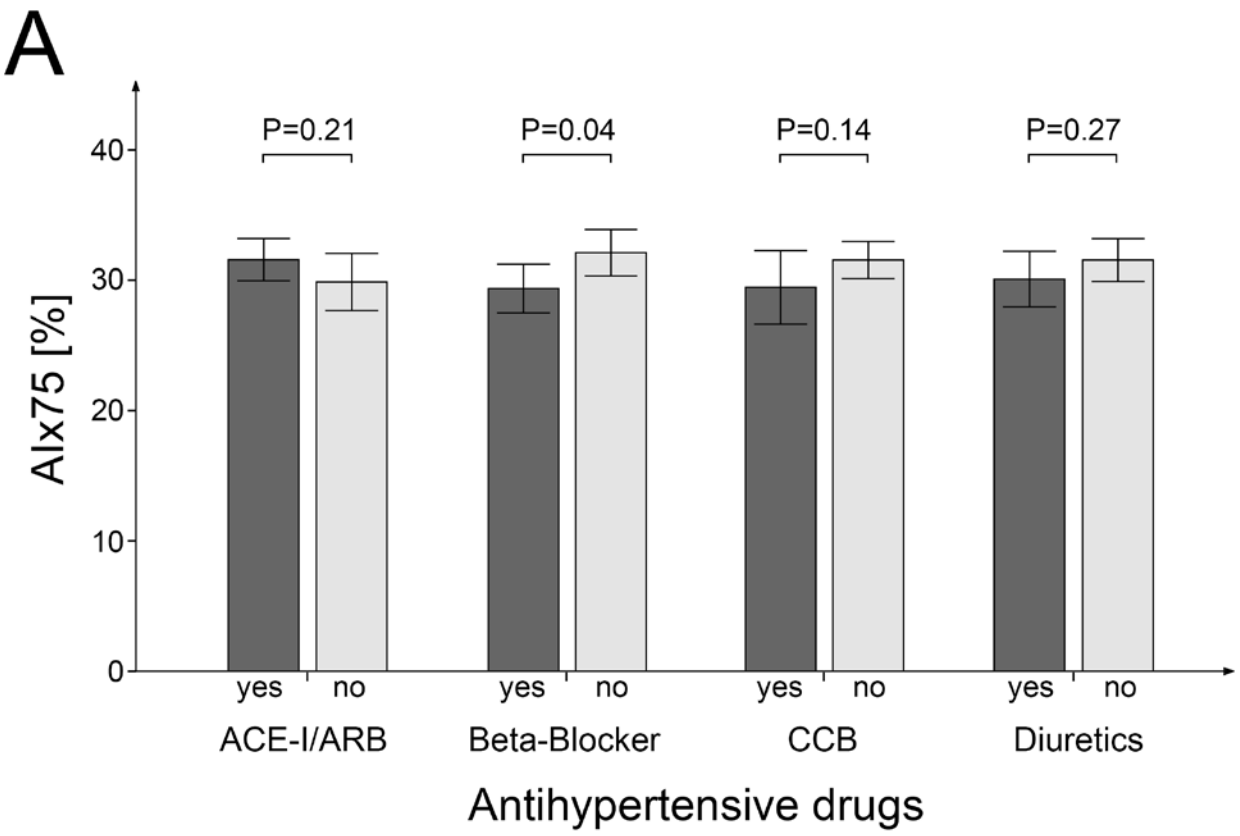
Figure 2

Bar charts (means) and respective error bars (± 2SE) illustrating the unadjusted augmentation index (AIx) vs. the heart rate adjusted augmentation index (AIx75) in patients with peripheral arterial disease receiving/not receiving beta blockers.

Figure 3

Bar charts (means) and respective error bars (± 2SE) illustrating the **(A)** aortic systolic blood pressure, **(B)** aortic diastolic blood pressure in patients with peripheral arterial disease receiving/not receiving angiotensin-converting enzyme inhibitors (ACE-I)/angiotensin receptor blockers (ARB), beta blockers, calcium channel blockers (CCB) and/or diuretics.

Figure 1.


A
P=0.21
P=0.04
P=0.14
P=0.27
AIx75 [%]
40
30
20
10
0
yes
no
ACE-I/ARB
Beta-Blocker
CCB
Diuretics
Antihypertensive drugs

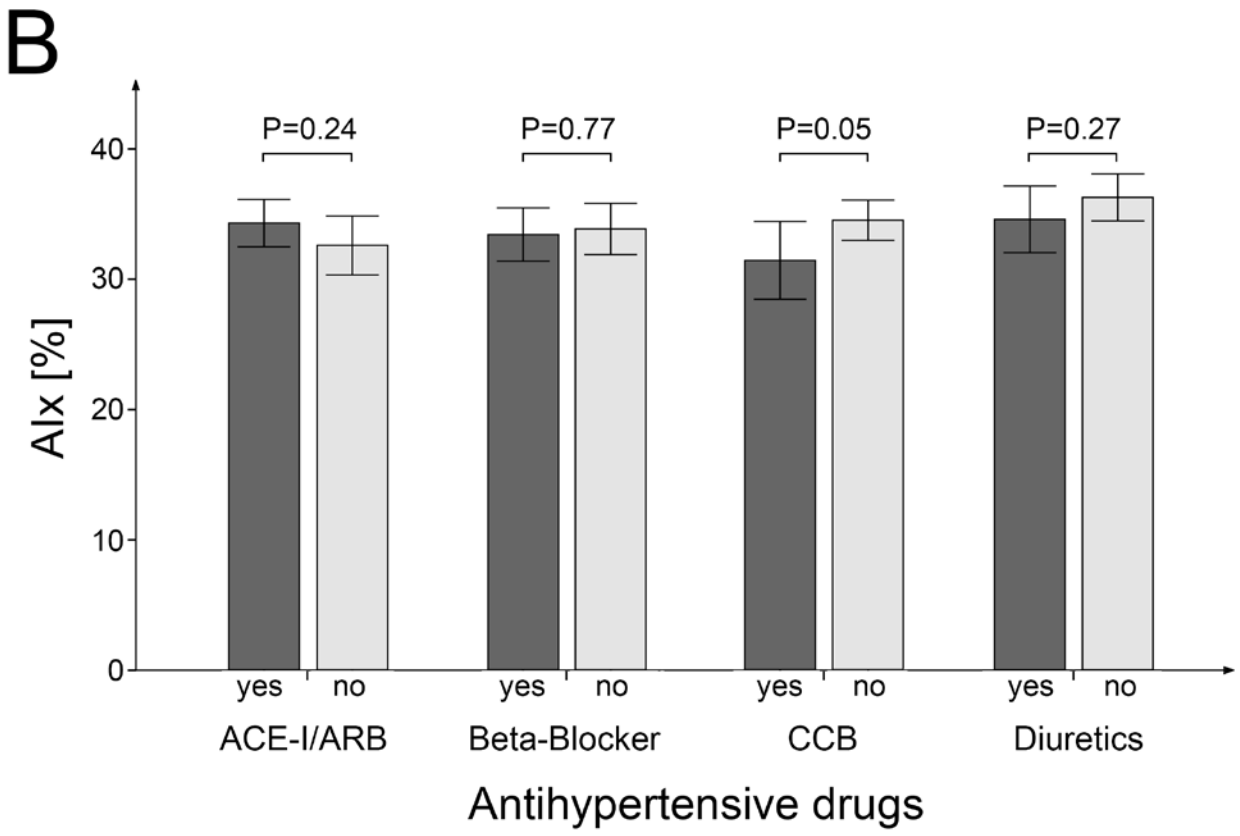

B
P=0.24
P=0.77
P=0.05
P=0.27
AIx [%]
40
30
20
10
0
yes
no
ACE-I/ARB
Beta-Blocker
CCB
Diuretics
Antihypertensive drugs

Figure 2.

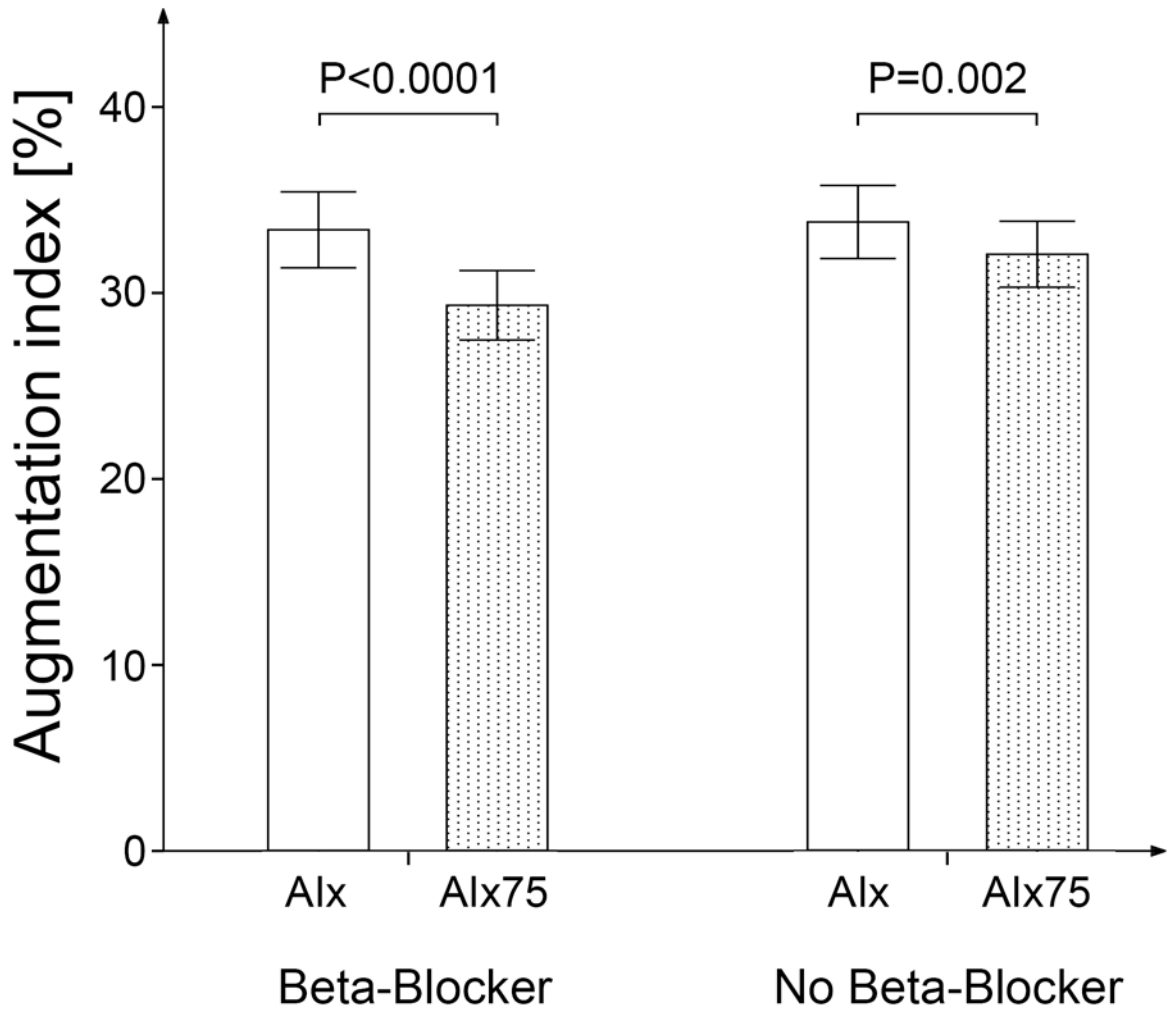
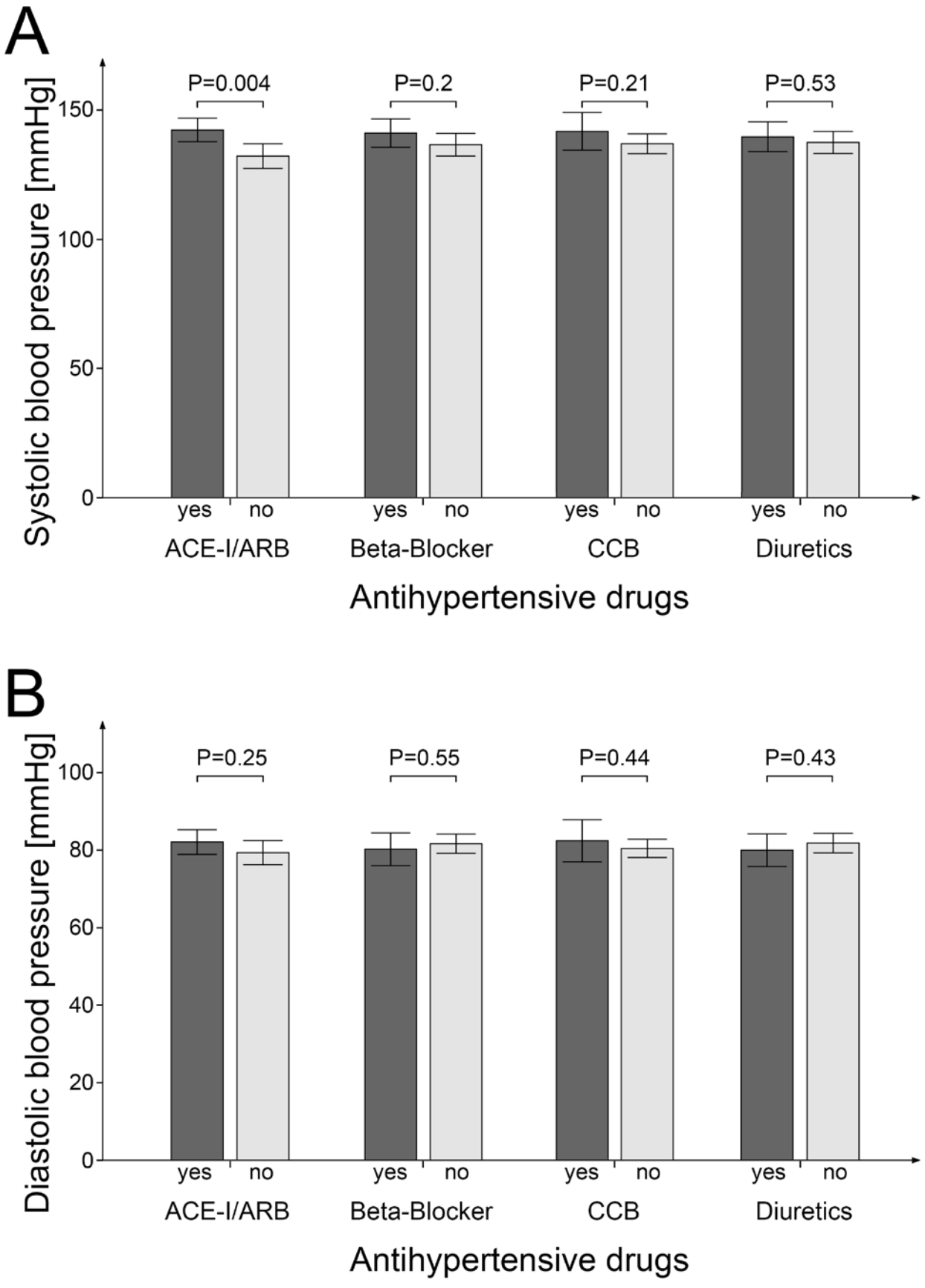

Augmentation index [%]
40
30
20
10
0
P<0.0001
P=0.002
AIx
AIx75
AIx
AIx75
Beta-Blocker
No Beta-Blocker

Figure 3.


A
Systolic blood pressure [mmHg]
150
100
50
0
P=0.004
P=0.2
P=0.21
P=0.53
yes
no
ACE-I/ARB
Beta-Blocker
CCB
Diuretics
Antihypertensive drugs
B
Diastolic blood pressure [mmHg]
100
80
60
40
20
0
P=0.25
P=0.55
P=0.44
P=0.43
yes
no
ACE-I/ARB
Beta-Blocker
CCB
Diuretics
Antihypertensive drugs